Critical Review Form
Meta-analysis
Does This Patient Have Influenza?
JAMA 2005; 293: 987-997

Objectives: "To identify clinical factors that may be valuable in distinguishing which patients with influenza-like illness have a higher probability of truly having influenza" (p.990). A secondary objective was to assess the usefulness of bedside diagnostic testing.

Methods: MEDLINE search (1966-2004 for clinical factors and 1996-2004 for diagnostic-testing) using a variety of exploded Medical Subject Headings (see p.989) and a review of previous systematic reviews, plus article reference lists. The authors did not search EMBASE, CINAHL, or Cochrane, nor did they contact influenza experts or relevant industries to identify additional published or unpublished data. Strict inclusion criteria of relevant manuscripts included:

  a) randomized controlled trial or meta-analysis
  b) primary assessment of individual clinical signs/symptoms as predictors of Influenza diagnosis
  c) Influenza (A or B) diagnosed by either culture, 4-fold increase in diagnostic antibody titer, polymerase chain reaction, or immunofluorescent antibody.
  d) Study Quality Grade A (independent, blinded comparison of signs and symptoms against criterion standard on at least 300 consecutive subjects) or B (independent, blinded comparison of signs and symptoms against criterion standard on less than 300 consecutive subjects).

Data from individual articles were used to calculate Likelihood Ratios and Diagnostic Odds Ratios. The LR's heterogeneity between studies was assessed using the Mantel-Haenszel Q-statistic. Summary Confidence Intervals used the conservative random-effects model to describe summary estimates.

Guide	Question	Comments
I	*Are the results valid?*	
1.	Did the review explicitly address a sensible question?	Yes – what impact do clinical signs and symptoms presence or absence have upon the probability of Influenza as the diagnosis.

Guide	Question	Comments
2.	Was the search for relevant studies details and exhaustive?	No, several search engines and strategies were neglected as noted above. Interestingly, the authors noted another recent systematic review which had identified studies they had missed (p.990).
3.	Were the primary studies of high methodological quality?	Yes. The authors' inclusion criteria and grading scale assured high methodological quality.
4.	Were the assessments of the included studies reproducible?	"Two of the authors independently reviewed the first set of 17 articles for quality" (p 989). However, they fail to describe reproducibility assessment (Kappa) or if discrepancies existed.
II.	*What are the results?*	(NEXT PAGE)

| 1. | What are the overall results of the study? | For the clinical features of Influenza, 915 articles were located, but only 10 met inclusion criteria. Four of these ten lacked original or primary data. So, six studies analyzed 7105 patients with the following findings:

• <u>Fever and cough are the most useful single findings for distinguishing patients with influenza from those without the illness among the unrestricted age groups</u>.

• <u>*Acute onset* fever and cough are the most helpful prediction of influenza among those **over age 60**</u>.

(See Table 1 below)

• For those over age 60, fever (LR+ 3.8), myalgia (2.4), malaise (2.6), headache (1.9), chills (2.6), fever & cough (5.0) and acute onset fever & cough (5.4) had significant discriminatory ability for the diagnosis of influenza.

Point-of-Care Tests
• For point-of-care tests, one published study assessed four commonly used commercial tests head-to-head in children with influenza-like illness. Sensitivity ranged 72-95% and Specificity ranged 76-84% with Summary LR+ 4.7 (95% CI 3.6-6.2) and LR- 0.06 (95% CI 0.03-0.12)

• The authors also summarized two cost-effectiveness analyses of empiric treatment vs. test-then-treat for influenza, noting that "if one is able to estimate the probability of influenza to be greater than 25 to 30%, rapid diagnostic testing does not add to the overall cost-effectiveness of treatment" (p.995). To estimate influenza prevalence at your institution logon to: www.cdc.gov/flu/weekly/fluactivity.htm. |
| 2. | How precise are the results? | "None of the studies assessed the precision of signs vs. symptoms of Influenza" (p.990) |

3.	Were the results similar from study to study?	No. Although statistically significant heterogeneity existed *between* studies, the "heterogeneity expressed in the confidence intervals never moved a finding from useless, to obviously useful", so the summary LRs and DORs were presented (p.991)
III.	*Will the results help me in caring for my patients?*	
1.	How can I best interpret the results to apply them to the care of my patients?	No single clinical finding or combination of findings can rule in or rule out Influenza. If in the midst of an Influenza season and your pre-test probability exceeds 25%, treat Influenza, if other etiologies of symptoms have been excluded. Below 25% pre-test probability rapid Influenza testing may play a role with the exception of Z-stat.
2.	Were all patient important outcomes considered?	No treatment consequences or outcomes were assessed. Presumably patients would want clinicians to be empowered to make the correct diagnosis using readily available data.
3.	Are the benefits worth the costs and potential risks?	On the basis of two prior cost-effectiveness analyses, testing for influenza is not more effective than empirically treating for influenza when the pre-test probability exceeds 30% (p.994). However, this was not the objective of the systematic review and is merely side-commentary.

Limitations

Incomplete search strategy.

Bottom Line

No symptom or combination of symptoms is diagnostic of Influenza, although the combination of acute onset fever and cough during flu season significantly increases the likelihood of Influenza in elderly individuals. The utility of rapid diagnostic testing likely varies throughout the Influenza season depending upon patient age and community-specific prevalence; rapid diagnostic tests are summarized at: www.cdc.gov/flu/professionals/labdiagnosis.htm and annual Influenza prevalence is maintained at www.cdc.gov/flu/weekly/fluactivity.htm

Table 1 – Symptom Diagnostic Characteristics for Influenza (All ages)

Symptoms	Sen. range	Spec. range	LR+	LR-	DOR
Fever	0.68 – 0.86	0.25 – 0.73	1.8 (1.1-2.9)	0.40 (0.25-0.66)	4.5
Cough	0.84 - 0.98	0.07 – 0.29	1.1 (1.1-1.2)	0.42 (0.31-0.57)	2.8
Feverishness	0.88	0.15	1.0 0.96-1.2)	0.70 (0.27-2.5)	1.3
Myalgia	0.60 – 0.94	0.06 – 0.38	0.93 (0.85-1.0)	1.2 (0.90-1.6)	0.79
Malaise	0.73	0.26	0.98 (0.75-1.3)	1.1 (0.51-2.2)	0.91
Headache	0.70 – 0.91	0.11 – 0.43	1.2 (0.9–1.7)	0.70 (0.38 – 1.3)	1.8
Sore Throat	0.75 – 0.84	0.16 – 0.33	1.0 (0.98-1.0)	0.96 (0.85-1.1)	1.1
Sneezing	0.33 – 0.50	0.59 – 0.69	1.2 (1.0-1.5)	0.87 (0.75-1.0)	1.3
Nasal Congestion	0.68 – 0.91	0.19 – 0.41	1.1 (1.1-1.2)	0.49 (0.42-0.59)	2.3
Chills	0.83	0.82	1.1 (1.0-1.2)	0.68 (0.46-0.99)	1.6
Vaccine History	0.12	0.83	0.71 (0.41-1.2)	1.1 (0.96-1.2)	0.69
Fever & Cough	0.64	0.67	1.9 (1.8-2.1)	0.54 (0.50-0.57)	3.6
Acute Onset Fever & Cough	0.63	0.68	2.0 (1.8-2.1)	0.54 (0.50-0.58)	3.6